HIPAA Compliant

Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals TREATMENT CONSENT This consent form contains ONE attachment.

H-39090- PREVALE- PHASE I STUDY COMBINING NIVOLUMAB WITH EPSTEIN BARR VIRUS SPECIFIC T CELLS (EB-STS) IN RELAPSED/REFRACTORY EBV POSITIVE LYMPHOMA PATIENTS

Background

In this consent form, "you" refers to you or your child. You are invited to take part in a research study. Please read this information and feel free to ask any questions before you agree to take part in the study. Your participation is completely voluntary. This is a consent form for an experimental treatment with a new drug called "Nivolumab" with cell therapy for lymphoma patients.

You have a type of a lymph node cancer called Hodgkin's lymphoma, Non-Hodgkin's lymphoma or lymphoproliferative disease (LPD), which affects your immunity, blood production, and can involve multiple other organs in your body. Your disease has come back or has not gone away after treatment. We are asking you to volunteer to be in a research study using an experimental treatment plan. The treatment plan consists of an antibody therapy called "Nivolumab" that helps your T-cells control the tumor, and special immune system cells called EBV-specific cytotoxic T lymphocytes, also a new therapy whose side effects are well studied.

Some patients with Hodgkin's lymphoma, Non-Hodgkin's lymphoma or LPD are infected with the virus that causes infectious mononucleosis (called Epstein-Barr virus, or EBV) before or at the time of their diagnosis. The cancer cells that are infected by EBV are able to hide from the body's immune system and escape destruction. We want to see if special white blood cells, called T cells, that have been trained to kill cells infected by EBV can survive in your blood and affect the tumor.

We have used this sort of therapy to treat a different type of cancer that occurs after bone marrow or solid organ transplant called post-transplant lymphoma with good success. These cells are called EBV-specific cytotoxic T-lymphocytes (EBVSTs), and are effective in treating these diseases. These EBVSTs are experimental and not yet approved by the Food and Drug Administration (FDA).

Sometimes it is not possible to grow these cells; or they may not last very long in the body after being given into the vein thereby having only limited time to fight your tumor. With this study, we aim to increase the duration of time that the T cells can last in the body and can effectively fight your cancer by using nivolumab. Nivolumab is FDA approved for treatment of Hodgkin's lymphoma and other kinds of cancer like lung cancer and a skin cancer called Melanoma. This medication is well tolerated by most patients when given into the vein every other week but may cause some side effects (fever, chills, allergic reaction, diarrhea, etc).

This research study is sponsored by Baylor College of Medicine. This research study is funded by Cell Medica.

Purpose

The purpose of this study is to find out if EBVST cells in combination with nivolumab are safe, to learn what the side effects are, and to see whether this therapy may help patients like you with EBV related lymphoma or LPD.

Procedures

The research will be conducted at the following location(s):

Patient ID	
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Up to 12 patients may be treated on this study.

Earlier you gave blood for us to make EBV-specific cytotoxic T-lymphocytes (EBVSTs) in the lab. We made the cells by first growing a special type of cells called dendritic cells (DCs) or monocytes to stimulate the T cells. We then added specially produced mixtures of proteins that included the LMP, EBNA1 and BARF proteins. These were used to stimulate T cells. As the T cells grew, we added some of your cells expressing these proteins to stimulate them. We also added a cell called K562 that has had new genes put inside it so it expresses proteins that stimulate the immune system to encourage the T cells to grow. K562 cells are cancer cells that have been treated with radiation so they cannot grow. This stimulation trained the EBVSTs to kill cells with EBV proteins on their surface. These cells were grown and frozen for you.

If you are considering this treatment, you will go through an evaluation for eligibility for the study which would involve a clinic visit to see the doctor, blood tests to check your how well your liver, kidney, heart and lungs are working, and also that your tumor has EBV on its surface.

The cells grown in the lab will be thawed and injected into your vein over 2-10 minutes. Before you receive the injection, you may be given Benadryl (diphenhydramine) and Tylenol (acetaminophen). Tylenol and Benadryl are given to prevent a possible allergic reaction to the T cell administration.

Initially, one dose of the drug nivolumab is given one day before the EBVST cells are infused (on day 0) and then every 2 weeks for a total of four doses of nivolumab. You will receive two infusions of the EB-VST cells. The first infusion will be given on Day 1 and you will receive a second infusion of T cells on Day 15.

If after this initial treatment with nivolumab and two doses of T cells, there is a partial reduction in the size of your lymphoma or you have stable disease (by physical exam or on a PET scan), you can receive up to three additional doses of the T cells 6-12 weeks apart and each additional T cell infusion would be preceded by one dose of nivolumab a day prior. All of the treatments will be given by the Center for Cell and Gene Therapy at Texas Children's Hospital or Houston Methodist Hospital.

TREATMENT PLAN

Nivolumab will be given over 1 hour into a vein every other week for four doses and repeated a day prior to any additional doses of T cells.

Two infusions of EBVST cells will be given 2 weeks apart. Three additional doses may be given 6-12 weeks apart based on response and if no side effects.

A diagram of the treatment plan is attached to this consent form. See TREATMENT CONSENT ATTACHMENT A.

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Standard medical tests before treatment:

Before being treated, you will receive a series of standard medical tests:

- Physical exam and History
- Blood tests to measure blood cells, kidney and liver function
- Pregnancy testing for female patients of childbearing potential (on blood or urine)
- Measurements of your tumor by scans and/or bone marrow studies will be performed as standard of care procedures
- Color photography of skin lesions to estimate the size of the lesion, if present

Standard Medical tests during and after treatment:

You will receive standard medical tests during and after study treatment:

- Physical exams and History
- Blood tests to measure blood cells, kidney and liver function
- Pregnancy testing for female patients of childbearing potential (on blood or urine) before each nivolumab dose
- Measurements of your tumor by PET scans and bone marrow studies 8 weeks after the first infusion per standard of care evaluation.
- Color photography of skin lesions to estimate the size of the lesion, if present

Study specific evaluations:

We will follow you closely after treatment for any side effects for at least for 1 year after your last infusion. To learn more about the way the T cells are working in your body, an extra 20-50 mL (4-10 teaspoons) of blood will be taken before the nivolumab infusion, before the EBVST infusion, 3- 5 days after the nivolumab infusion (optional), at week 1, 2, 4 and 6 and 3, 6, 9 and 12 months after the first nivolumab infusion. For patients < 18 years, a maximum of 3mL/kg of blood will be taken on one occasion.

The blood may be drawn from your central line at the time of your regular blood tests. We will use this blood to see how long the T cells last and to look at the immune response to your cancer.

If you are eligible and choose to receive additional doses of T cells after your first two infusions, you will have these same tests before each nivolumab infusion, before each EBVST infusion and at 2, 4, and 6 weeks after each nivolumab infusion.

If you have a biopsy of your tumor or bone marrow studies while on study, we may ask to have a piece of tumor or bone marrow to look for tumor cells or EBVSTs.

In the event of death, we will request permission to perform an autopsy to learn more about the effects of the treatment on your disease. This consent form is not legally binding and proper consent for an autopsy will be obtained from your next of kin in the event of your death.

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If you decide to withdraw at any time during the study both samples and data collected during your participation will be maintained.

Research related health information

Authorization to Use or Disclose (Release) Health Information that Identifies You for a Research Study

If you sign this document, you give permission to people who give medical care and ensure quality from Baylor College of Medicine, TCH: Texas Children's Hospital, and TMH: The Methodist Hospital to use or disclose (release) your health information that identifies you for the research study described in this document.

The health information that we may use or disclose (release) for this research includes:

- Information from health records such as diagnoses, progress notes, medications, lab or radiology findings, etc.
 - Specific information concerning HIV
 - · Demographic information (name, D.O.B., age, gender, race, etc.)
 - · Billing or financial records
 - · Photographs, videotapes, and/or audiotapes of you

The health information listed above may be used by and or disclosed (released) to researchers, their staff and their collaborators on this research project, the Institutional Review Board, Baylor College of Medicine, TCH: Texas Children's Hospital, TMH: The Methodist Hospital, and CELL MEDICA, LTD and their representatives.

Agents of the U.S. Food and Drug Administration may inspect the research records including your health information. Agents of regulatory agencies such as the U.S. Department of Health and Human Services will be permitted to inspect the research records including your health information.

A Data and Safety Monitoring Board will have access to the research records including your health information.

Use or Disclosure Required by Law

Your health information will be used or disclosed when required by law.

Your health information may be shared with a public health authority that is authorized by law to collect or receive such information for the purpose of preventing or controlling disease, injury, or disability and conducting public health surveillance, investigations or interventions.

Baylor College of Medicine, TCH: Texas Children's Hospital, and TMH: The Methodist Hospital are required by law to protect your health information. By signing this document, you authorize Baylor College of Medicine, TCH: Texas Children's Hospital, and TMH: The Methodist Hospital to use and/or

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disclose (release) your health information for this research. Those persons who receive your health information may not be required by Federal privacy laws (such as the Privacy rule) to protect it and may share your information with others without your permission, if permitted by laws governing them.

Please note that the research involves treatment. You do not have to sign this Authorization, but if you do not, you may not receive research-related treatment. To maintain the integrity of this research study, you generally will not have access to your personal health information related to this research until the study is complete. However, your health information that is necessary to your care will be provided to you or your physician. At the conclusion of the research and at your request, you generally will have access to your health information that Baylor College of Medicine, TCH: Texas Children's Hospital, and TMH: The Methodist Hospital maintain in a designated record set, which means a set of data that includes medical information or billing records used in whole or in part by your doctors or other health care providers at Baylor College of Medicine, TCH: Texas Children's Hospital, and TMH: The Methodist Hospital to make decisions about individuals. Access to your health information in a designated record set is described in the Notice of Privacy Practices provided to you by representatives of the specific institution where you are being enrolled into this research study which are: Baylor College of Medicine, TCH: Texas Children's Hospital, and TMH: The Methodist Hospital.

Please note that you may change your mind and revoke (take back) this Authorization at any time. Even if you revoke this Authorization, researchers, their staff and their collaborators on this research project, the Institutional Review Board, CELL MEDICA, LTD and their representatives, regulatory agencies such as the U.S. Department of Health and Human Services, FDA, Baylor College of Medicine, Data and Safety Monitoring Board, TCH: Texas Children's Hospital, and TMH: The Methodist Hospital may still use or disclose health information they already have obtained about you as necessary to maintain the integrity or reliability of the current research. If you revoke this Authorization, you may no longer be allowed to participate in the research described in this Authorization.

To revoke this Authorization, you must write to: Dr. RAVI PINGALI, 6445 Main Street, OPC 24, Houston, TX 77030.

This authorization does not have an expiration date. If all information that does or can identify you is removed from your health information, the remaining information will no longer be subject to this authorization and may be used or disclosed for other purposes.

No publication or public presentation about the research described above will reveal your identity without another authorization from you.

Potential Risks and Discomforts

a) Risks of T Cell treatment:

Most patients have no or few side effects. In some patients with large tumors, the cells have caused inflammation leading to fever and flu-like symptoms as well as swelling at the tumor site. This swelling could be potentially dangerous and even life threatening depending on the site. There is a possibility

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that body organs like the liver or kidney could be damaged if the cells cause inflammation.

Another risk is that the EBV virus itself will be injected with the T cells and you may have another active infection. We think this is very unlikely and we have also tested the T cells before we use them to reduce the likelihood that any of the cells that we have infected with EBV will be injected with the T cells.

As the T cells will be grown for several days after contact with the stimulator cells (K562 cells or your cells with the EBV proteins) it is possible that these cells could be injected with your T cells. K562 cells are cancer cells. As such they could cause cancer. This is unlikely because we will test the T cells before we use them and we will also wash the cells several times so there should not be any protein remaining. However, we cannot completely exclude this possibility.

A small percentage of patients that receive this type of therapy develop a life threatening complication known as cytokine release syndrome (CRS). This complication causes high body temperature, increased heart rate, and low blood pressure. This complication can be life threatening, but you will be monitored carefully for development of this complication. There are treatments for this complication.

b) Risks of Nivolumab:

Most common side effect seen (at least 20% and more) in patients with melanoma treated with nivolumab was skin rash. Side effects were noted 40-50% of patients in previous studies, with <10% patients having severe side effects needing discontinuation of treatment. Side effects from mild to very serious occurred in almost half (41-50%) of the patients. However the serious side effects were seen in <10% of patients. The most frequent side effects reported in 2% to less than 5% of patients were belly pain, low sodium, abnormal liver function tests and inflammation of the pancreas. Similarly most common side effects seen (at least 20% and more) in patients treated for lung cancer were tiredness, shortness of breath, muscle/joint pain, decreased appetite, cough, nausea, and constipation. The most frequent serious adverse reactions reported in at least 2% of patients were shortness of breath, pneumonia, Chronic Obstructive Pulmonary Disease (COPD) exacerbation, high calcium, throwing up blood and pain.

Other Risks

Possible side effects from drawing blood may include pain or bruising at the site of the needle. There is a very small risk of an infection at the site of the needle puncture. Also, it is possible that a person may faint when blood is drawn. Care will be taken to clean the site well and therefore decrease the risk of infection.

Acetaminophen (Tylenol): Rarely large doses or long-term usage can cause liver damage, rash, itching, fever, lowered blood sugar. These side effects are unlikely at the doses being used for this study.

Risks of Benadryl include drowsiness, dizziness, headache, irritability, stomach upset, vision changes

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(e.g., blurred vision), decreased coordination, or dry mouth/nose/throat may occur.

Because of potential or unknown effects of the study on a fetus, if you are a woman of child-bearing potential, you must have a negative serum pregnancy test prior to entry into this study.

Risks of combination therapy are unknown. Since this is a research study we will watch you very carefully for any side effects. If there are bad side effects, we will stop the treatment.

There may be unknown risks or discomforts involved. Study staff will update you in a timely way on any new information that may affect your decision to stay in the study. There is a small risk for the loss of confidentiality. However, the study personnel will make every effort to minimize these risks.

Potential Benefits

The benefits of participating in this study may be: that your immune system will be boosted by nivolumab which may help to kill the EBV infected cancer cells and B cells, making the lymphoma go away. However, you may receive no benefit from participating.

Alternatives

The following alternative procedures or treatments are available if you choose not to participate in this study: no further treatment, or other treatment with other drugs used to treat your condition (which for cancer patients may include chemotherapy and radiation). Your doctor will discuss these other options with you. Additionally, the same alternatives are available during participation in this research project.

Subject Costs and Payments

You will not be charged for the manufacture or preparation of the T cell injections, for the drug nivolumab, or any evaluations that are being done solely as part of your participation in this research project. You or your insurance company may be charged for some research related costs including the infusion of the T cell product. You will be charged for any tests or treatments that are being done as standard treatment for your disease.

You will not be paid for taking part in this study.

This institution does not plan to pay royalties to you if a commercial product is developed from blood or tissue obtained from you during this study.

Research Related Injury

If you are injured as part of your participation in this study, there are no plans to pay you.

Research personnel will try to reduce, control, and treat any complications from this research. If you are injured because of this study, you will receive medical care that you or your insurance will have to pay for just like any other medical care.

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Women of Childbearing Potential

It is possible that the medicines used in this study could injure a fetus if you or your partner becomes pregnant while taking them. Because of the potential risks involved, you or your partner should not become pregnant while you are participating in this study.

If you are sexually active or become sexually active and can get pregnant or can get your partner pregnant, you must agree to use one of the following forms of birth control every time you have sex and for (6) months afterwards:

- * oral contraceptives ("the pill"),
- * intrauterine devices (IUDs),
- * contraceptive implants under the skin, or contraceptive injections,
- * condoms with foam.

Should you become pregnant while on this study, you must immediately notify the study personnel.

The investigator will assist you in finding appropriate medical care. The investigator also may ask to be allowed to continue getting information about your pregnancy. You can choose not to provide this information.

Subject's Rights

Your signature on this consent form means that you have received the information about this study and that you agree to volunteer for this research study.

You will be given a copy of this signed form to keep. You are not giving up any of your rights by signing this form. Even after you have signed this form, you may change your mind at any time. Please contact the study staff if you decide to stop taking part in this study.

If you choose not to take part in the research or if you decide to stop taking part later, your benefits and services will stay the same as before this study was discussed with you. You will not lose these benefits, services, or rights.

The investigator, HELEN E. HESLOP, and/or someone he/she appoints in his/her place will try to answer all of your questions. If you have questions or concerns at any time, or if you need to report an injury related to the research, you may speak with a member of the study staff: SAI RAVI KIRAN PINGALI at 713-441-6220 during the day and 713-441-1450 after hours.

Members of the Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals (IRB) can also answer your questions and concerns about your rights as a research subject. The IRB office number is (713) 798-6970. Call the IRB office if you would like to speak to a person independent of the investigator and research staff for complaints about the research, if you cannot reach the research staff, or if you wish to talk to someone other than the research staff.

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The National Institutes of Health and the National Cancer Institute may have access to your records for research purposes.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

ADULT ASSENT (as applicable)

If the person you represent is the one invited to take part in this study, you are signing to give your permission. Each adult who lacks the capacity to consent may agree to take part in a study at his or her own level of understanding. When you sign this, you also note that the person you legally represent understands and agrees to take part in this study according to his or her understanding.

Please print the person name you legally represent here
If your child is the one invited to take part in this study you are signing to give your permission. Each child may agree to take part in a study at his or her own level of understanding. When you sign this you also note that your child understands and agrees to take part in this study according to his or her understanding.
Please print your child's name here

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Signing this consent form indicates that you have read this consent form (or have had it read to you), that your questions have been answered to your satisfaction, and that you voluntarily agree to participate in this research study. You will receive a copy of this signed consent form.

Subject	Date	
Legally Authorized Representative Parent or Guardian	Date	
Legally Authorized Representative - Adult	Date	
Investigator or Designee Obtaining Consent	Date	
Witness (if applicable)	Date	
Translator (if applicable)	Date	

H-39090 PREVALE Treatment Consent Attachment A

